REMARKS

Upon entry of the present amendment, claims 144, 156-168, 170-204, and 206-218 will be pending. Claims 144, 159, 172, 178, 180, 184, and 185 have been amended to incorporate the limitation "binds to prostate specific membrane antigen (PSMA)". Support for these amendments can be found in the original claims. Claim 181 has been amended to incorporate the subject matter of claim 205 which has been cancelled. Claim 204 has been amended specify the limitation "wherein the prostate cancer is metastasized". Support for this amendment can be found at page 1, lines 25-26 of the specification. New claims 211-218 have been added. Support for these claims can be found in the previously pending claims. Applicant submits that no new matter has been added.

Ownership

In the Office Action dated April 11, 2007 (the "Office Action"), claims 144, 156-168, 170-178, and 180-210 were alleged to be patentably indistinct from claims 1-142 of commonly assigned U.S. Patent No. 7,045,605. These applications/patents were owned by the same person as required by 35 U.S.C. § 103 (c) (1).

Objections to the Specification

The Examiner objects to the specification because at page 1, paragraph 1, the specification does not properly indicate the status of Application Serial No. 08/838,682, which has issued as U.S. Patent No. 6,107,090. Applicant has amended the specification accordingly.

Priority

According to the Examiner, "the effective date of claims 144, 156-168 and 170-210 is deemed the filing date of the instant application, namely August 13, 2001" because these claims "are rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and/or a sufficiently enabling disclosure" (at page 5). In view of the arguments and claim

amendments below, Applicants submit that these claims are entitled to the earliest priority date of May 6, 1996. Acknowledgement of the earliest priority date is respectfully requested.

Rejections under 35 U.S.C. § 112, Second Paragraph

The Examiner rejects claims 144, 156-168, and 170-210 as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. According to the Examiner, these claims are indefinite:

> because of the recitation in claim 144, for example, of "which competes for binding to prostate specific membrane antigen (PSMA) with a monoclonal antibody" selected from the specified group of monoclonal antibodies. (at page 6)

The Examiner discusses an art-known word "competes" in detail at pages 7-9, and concludes that:

> the claims are not unambiguously interpreted, as it cannot be determined whether the antibody to which the claims are directed is an antibody that merely inhibits, but does not abrogate the interaction between the selected antibody and PSMA. Moreover, if the claimed antibody merely inhibits binding of the selected antibody to PSMA, it cannot be determined to what requisite extent the claimed antibody must "compete" for binding to PSMA with the selected antibody (at page 9; emphasis in original).

Applicants respectfully disagree with this assertion. The term "competes" for binding as recited in the claims is not ambiguous. A skilled artisan at the time the present application was filed would be able to determine if an antibody competes for binding with the deposited antibodies. Further, Applicants respectfully disagree with the Office's characterization of George et al. (Circulation. 1998; 97:900-906) ("George"), cited in support of the Office's arguments. According to the Examiner at page 9,

> George et al. illustrates the capricious and arbitrary nature of determinations that different antibodies bind to the same or different epitopes, which are based upon the results of competitive binding assays, such as the assays exemplified in the specification. Although each of the described antibodies "competed" to a measurable extent with the other antibodies for binding to the antigen, George et al. nevertheless concludes "no competition was achieved", and the antibodies bind distinct, non-overlapping epitopes.

Applicants respectfully disagree with this assertion. First, this assertion misses the point of the competition limitation, which merely defines a group of antibodies within the invention, namely those antibodies that compete. Furthermore, competition binding assays were used routinely in the art at the time of filing and a determination of whether an antibody competes for binding with another antibody could be objectively and clearly made by one of ordinary skill in the art at the time of filing. Competition binding assays compare the ability of a first antibody to interfere with binding of a second antibody to its antigen. Such assays can be taken to saturating conditions, and antibodies that do not interfere with binding of the second antibody to its antigen within a reasonable margin of error are considered non-competing antibodies, while those that do displace the second antibody completely or almost completely are considered competing antibodies. This was an accepted and well-understood practice at the time the present application was filed.

Contrary to the assertions made in the Office Action, George further demonstrates this point. Based upon results that showed that an antibody did not interfere with binding of the second antibody to its antigen within a reasonable margin of error, George concludes that the antibodies do not compete for binding. While the Office Action alleges that this is arbitrary, George provides no indication that this determination was subjective. In fact, George makes no attempt to rationalize the determination that the antibodies do not compete for binding (at page 903, paragraph bridging the first and second columns). That is because the results speak for themselves and would be clear to a skilled artisan reviewing that reference.

The Office also stated that "[a]lthough each of the described antibodies 'competed' to a measurable extent with the other antibodies for binding to the antigen, George et al. nevertheless concludes that 'no competition was achieved'" (at page 9, within quote above). Applicants are at a loss as to why the Office disputes the conclusions of George and contends that George's antibodies do compete with one another. George carried out scientific experiments and determined that a reasonable threshold for competition, e.g., 5-9% inhibition, indicated no competition (page 903 first and second cols.). As discussed above, George does not rationalize the choice of the threshold, because the results are clear to a skilled practitioner.

The Office also made the following assertions:

> [I]t is recognized that the degree of binding of an antibody, which is observed in the exemplified competitive binding assay, will depend upon the concentration of the detectably labeled antibody and the unlabeled competing antibody. Typically, the higher the concentration of the unlabeled competitor, the lower the percentage of binding of the labeled antibody. So, at *high enough* concentrations, any antibody might be deemed capable of "competing" for binding to an antigen with any other antibody, regardless of whether or not the different antibodies bind to the same, or even overlapping epitopes (at page 8, emphasis in original).

Applicants respectfully disagree. Skilled practitioners routinely carry out planned and controlled experiments to determine whether antibodies compete with one another. They would not arbitrarily add a concentration of an antibody so high as to give false positive results (which seem to be described in the quote above) without testing other concentrations. In fact, the George reference cited by the Examiner, exemplifies standard competition experiments. According to George, "each of the nonbiotinylated mAbs (or control IgM) was used as competitors for binding in different concentrations (0 to 100μg/mL) to the single biotinylated mAb (at concentration giving 50% maximal binding) in the anti-β2GPI ELISA" (at page 901, second col.). Percentage of inhibition was calculated according to a standard equation (Id.). Thus, George's experiments were carried out with a standard concentration of one antibody and varying concentrations of other antibodies tested for competition. The variables and the controls were planned out according to accepted scientific procedures. Applicants submit that, like George, skilled practitioners would appreciate how to carry out competition assays without obtaining false positives and thus understand the claimed features.

A determination of whether or not an antibody competes for binding with another antibody was a well-established procedure at the time of filing. In addition, interpretation of such assays to determine whether antibody competes or does not compete for binding was a well-established practice. George exemplifies this by making an affirmative decision that an antibody does or does not compete based upon that fact that a first antibody did not interfere within a reasonable margin of error for the binding of a second antibody to its antigen. A skilled

artisan could easily make such a determination and thus clearly know the metes and bounds of the present claims.

Rejections under 35 U.S.C. § 112, First Paragraph

New matter

Claims 178, 179, 181-183, 204, 206, and 207 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The Examiner alleges that the claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor had possession of the claimed invention at the time the application was filed. The rejection has been met, in part (as will be described subsequently), by amending the claims. Applicants also traverse this rejection in part.

At page 10 of Office Action, the Office specifically pointed out that claims 178 and 179 are directed to a genus of "cells" that produce antibodies that compete for binding to PSMA with a selected monoclonal antibody and that claim 179 is more particularly directed to members of this genus, which are derived from a lymphocytic cell line. The Office (at page 11 of the Office Action) indicated that while the originally filed disclosure describes the deposited hybridomas that produced monoclonal antibodies E99, J415, J533, and J591, that it

> does not describe with any degree of particularity a genus of 'cells' that produce an antibody that competes for binding to PSMA with any of the monoclonal antibodies produced by those hybridomas.

The written description requirement is met if the specification shows that an applicant was in possession of the claimed invention at the time of filing. "When the original specification accomplishes [this], regardless of *how* it accomplishes it, the essential goal of the description requirement is realized." *In re Smith*, 481 F.2d 910, 914 (CCPA 1973). It is well accepted that "in order to satisfy the written description requirement, the disclosure as originally filed does not have to provide *ad haec verba* support for the claimed subject matter at issue". *Purdue Pharma v. Faulding, Inc.*, 56 USPQ 2d 1481 (Fed. Cir. 2000); and MPEP § 2163.02. As provided, for

example, in *In re Wright*, 866 F.2d 422 (Fed. Cir. 1989), "the fact... that the exact words here in question... are not in the specification is not important" (emphasis added).

Here, the original disclosure clearly shows that Applicant was in possession of cells that produce antibodies that compete for binding to PSMA with monoclonal antibodies E99, J533, and J591 produced by ATCC designated hybridoma cell lines HB-12101, HB-12127, and HB-12126 respectively as shown in Table 1 (at page 19 of the specification as filed). These hybridoma cell lines were made by the Applicant (therefore, in his possession) and under "Example 10 – Competition Studies" (specification at page 37, line 24 through page 39, line 14), the specification indicates that the antibodies produced by hybridoma cell lines HB-12101, HB-12127, and HB-12126 (E99, J533, and J591 respectively) compete with each other for binding to PSMA whereas antibody produced by HB-12109 (J415) does not compete with E99, J533, or J591 for binding to PSMA. The specification, makes clear that each monoclonal antibody competes with itself for binding to PSMA. In Applicant's experiment described in Example 10 "[c]ontrols consisted of using the same monoclonal antibody both cold and labeled to define '100% competition'" (specification at page 38, lines 5-6). Thus, the specification shows that Applicant was in possession of hybridoma cells (HB-12101, HB-12109, HB-12127, and HB-12126) that meet the necessary limitations as recited in currently amended claim 178:

> An isolated cell which produces an antibody which binds to prostate specific membrane antigen (PSMA) and competes for binding to PSMA with a monoclonal antibody selected from the group consisting of a monoclonal antibody produced by a hybridoma deposited under ATCC deposit accession number HB-12101, a monoclonal antibody produced by a hybridoma deposited under ATCC deposit accession number HB-12109, a monoclonal antibody produced by a hybridoma deposited under ATCC deposit accession number HB-12127 and a monoclonal antibody produced by a hybridoma deposited under ATCC deposit accession number HB-12126.

Further, the skilled practitioner would recognize that Applicant was in possession of lymphocytes producing antibodies that compete for binding to PSMA with the above-specified monoclonal antibodies. The production of monoclonal antibodies is routine in the art (and described in the specification from page 6, line 5 to page 18, line 10). The skilled practitioner would recognize that monoclonal antibodies are generated by immortalizing an antibody-

producing lymphocyte isolated from the spleen of an immunized mammal to produce a clonal population of antibody-producing cells (the hybridoma cell line). The skilled practitioner would recognize that antibodies produced by the progenitor lymphocyte and derivative hybridoma have the same epitope specificity and that the hybridoma cells are derived from a lymphocyte cell line.

Thus, the originally filed disclosure demonstrates that the Applicant was in possession of at least four-different hybridoma cell lines and at least four-different lymphocytes (from which the hybridoma cell lines were derived) and a skilled practitioner would understand that all of these produced antibodies that would compete for binding to PSMA with at least one of the monoclonal antibodies recited in claim 178. The skilled practitioner would also recognize that the hybridoma cell lines are each derived from a "lymphocytic cell line" as recited by claim 179 and that Applicant was in possession of these hybridoma cell lines which meet the limitations of claims 178 and 179. For at least these reasons, Applicant requests that the rejection of claims 178 and 179 for lack of written description be withdrawn.

Claims 181-183, 204, 206, and 207 have been rejected at page 12 of the Office Action for lack of written description support for "kits for detecting any of a genus of different type of cancer, with the notable exception of a kit for detecting prostate cancer," (Office Action at page 12). Applicant has amended claims to read as follows: "[a] kit for detecting prostate epithelial cells comprising: an antibody or antigen binding portion thereof according to claim 172 and means to detect the label." This amendment obviates the rejection.

Written description

The Office Action at page 13 indicates that claims 144, 156-168, and 170-210 are rejected for failing to comply with the written description requirement. According to the Office, "[t]he claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention," (Office Action at page 13).

The Office has variably rejected the claims based on the premise that the specification fails to demonstrate possession of a genus of antibodies that

> competes for binding to PSMA with a monoclonal antibody selected from the group consisting of a monoclonal antibody produced by a hybridoma deposited under ATCC deposit accession number HB-12101, a monoclonal antibody produced by a hybridoma deposited under ATCC deposit accession number HB-12109, a monoclonal antibody produced by a hybridoma deposited under ATCC deposit accession number HB-12127 and a monoclonal antibody produced by a hybridoma deposited under ATCC deposit accession number HB-12126, (e.g., claim 144).

According to the Office, at page 17 of the Office Action,

> It is submitted that the disclosure would not reasonably convey to the skilled artisan that Applicant had possession of the claimed subject matter at the time the application was filed because it fails to adequately describe the genus of antibodies or antigen-binding fragments that bind specifically to PSMA and thereby "compete" for binding to the antigen with any one of the recited monoclonal antibodies.

Contrary to the assertions made in the Office Action, it is Applicants position that the Office that the Board of Patent Appeals and Interferences has already decided in favor of the Applicant on this matter. The Board, at page 4 of the Decision on Appeal, stated the following which is relevant here:

> "The 'written description' requirement serves a teaching function,... in which the public is given 'meaningful disclosure in exchange for being excluded from practicing the invention for a limited period of time.'" University of Rochester v. G.D. Searle & Co., Inc., 358 F.3d 916, 922, 69 USPQ2d 1886, 1891 (Fed. Cir. 2004) (citation omitted). Another "purpose of the 'written description' requirement is... [to] convey with reasonable clarity to those skilled in the art that, as of the filing date [], [the applicant] was in possession of the invention." Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). See also Enzo Biochem Inc. v. Gen-Probe Inc., 296 F.3d 1316, 1329, 63 USPQ2d 1609, 1617 (Fed. Cir. 2002). The requirement is satisfied when the specification "set[s] forth enough detail to allow a person of ordinary skill in the art to understand what is claimed and to recognize that the inventor invented what is claimed." University of Rochester, 358, F.3d at 938, 69 USPQ2d at 1896. Whether or not a specification satisfies the requirement is a question of fact, which must be resolved on a case-by-case basis (Vas-Cath, 935 F.2d at 1562-63, 19 USPQ2d at 1116).

Based on this understanding of the written description requirement (which encompasses issues relating to the introduction of new matter but is not restricted to them), the Board stated, "we agree with the appellant that the specification describes the disputed subgenus of antibodies," (page 4 of the Decision on Appeal) wherein the subgenus of antibodies is defined as "a subgenus of antibodies that 'compete for binding' to E99, J591, J415, or J533" (page 3 of the Decision on Appeal). The Board concluded that

> appellant's disclosure as a whole reasonably conveys to one of skill in the art that appellant was in possession of '[a]n isolated antibody or antigen binding portion thereof which competes for binding to prostate specific membrane antigen [] with a monoclonal antibody selected from the group consisting of an E99, a J415, a J533 and a J591 monoclonal antibody" (claim 144), as of the filing date of this application.

As acknowledged by the Board, the essence of the written description requirement (whether it relates to new matter or not) is that the invention is disclosed in such a way that a skilled practitioner would understand that the Applicant was in possession of the invention at the time of filing of the disclosure. The Board has acknowledged that the disclosure fulfills the written description requirement for the "subgenus" of antibodies claimed.

Although the Board has decided that the disclosure demonstrates that Applicant was in possession of the invention, the Office Action essentially reiterated the arguments presented under the Indefiniteness rejections regarding the determination of whether "the antibody 'competes' for binding to PSMA with any one of the recited monoclonal antibodies" and concludes that "the requisite degree to which the claimed antibody or antigen binding fragment 'competes' with any other member of the recited pluralities of monoclonal antibodies for binding to PSMA is not specified in the claims, and is not ascertainable from the disclosure." The Office again cites George for its arguments (at page 14).

Contrary to the assertions made in the Office Action, George does not teach "that even antibodies that decidedly do not bind overlapping epitopes are able to compete to some measurable extent with other antibodies that bind the same antigen," (Office Action at page 14). On the contrary, George comes to the conclusion that "the three mAbs target different non-cross-

reactive epitopes" (George at page 903, 2nd col.) based upon results that showed that one antibody did not interfere with binding of another antibody to its antigen within a reasonable margin of error. Based on their finding that the antibodies do not compete for binding, they concluded that the antibodies bind different epitopes. In fact, George takes the knowledge of the skilled practitioner so much for granted that they make no attempt to rationalize the determination that the antibodies do not compete with each other for binding to the antigen (at page 903, paragraph bridging the first and second columns).

Further, the Office rejected the claims alleging that the disclosure does not describe the genus of antibodies claimed in terms sufficient to demonstrate possession of the genus. First, the Office Action at page 16

> submitted that there is inadequate description of the claimed genus of antibodies or antigen-binding fragments that compete for binding to PSMA with monoclonal antibody J415 to reasonably convey Applicant's possession of the claimed invention at the time the application was filed. Again, none of the monoclonal antibodies J591, J533, E99, and 7E11/CYT356 are described as having the ability to "compete" for binding to PSMA with monoclonal antibody J415.

Applicant would like to point out that the disclosure, in fact, demonstrates possession of at least one member of the genus of antibodies or antigen-binding fragments that compete for binding to PSMA with monoclonal antibody J415, namely J415 labeled with either biotin or ^{125}I as indicated by the specification at page 37, line 35. As indicated by the specification at page 35, lines 5-10 describing binding competition assays, "[c]ontrols consisted of using the same monoclonal antibody both cold and labeled to define '100% competition'... or using monoclonal antibody to a totally different molecule... to define '0%' competition." Thus, Applicant submits that the disclosure demonstrates possession of at least one of biotin or ^{125}I labeled J415 falling within the genus and ask that claim rejections on this premise be withdrawn.

Second, the Office rejected the claims because the specification "fails to adequately describe the genus of antibodies or antigen-binding fragments that bind specifically to PSMA and thereby 'compete' for binding to the antigen with any one of the recited monoclonal antibodies," (Office Action at page 17). The claims have been amended to recite the limitation

"[a]n isolated antibody or antigen binding portion thereof which binds to prostate specific membrane antigen".

The Office entered into a lengthy discussion on epitopes and how epitopes are defined (Office Action at pages 17-21). In particular, the Office cited George as evidence that "antibodies need not bind the same epitope, or even an overlapping epitope of an antigen to 'compete' with another antibody for binding to the antigen," (Office Action at page 18). Further, the Office stated that defining epitopes is "not as easy as it seems" (Office Action at page 20) and cited Greenspan et al. (Nature Biotechnology, 7:936-937, 1999), herein "Greenspan." as indicating that "structural characterization of the molecular interface between the antigen and the antibody is necessary to define an 'epitope'" (Office Action at page 20).

Applicant submits that the term "epitope" is absent from the claims and that the Office is unnecessarily reading this limitation into the claims.

Greenspan is a review article that focuses on one method for assigning binding epitopes for antigen-antibody or receptor-ligand interactions. The method involves generating alanine substituted mutants of one partner in a binding pair (e.g. antigen-antibody or receptor-ligand) and determining the difference in binding free energy between mutant and wildtype. Greenspan is completely silent as to antibodies that compete for binding to an antigen and is not relevant to the rejected claims.

For at least these reasons, Applicant requests that the rejection be withdrawn.

Enablement

Claims 144, 156-168, and 170-210 are rejected under 35 U.S.C. 112, first paragraph. According to the Office Action at page 23,

> the specification, while being enabling for making and using a monoclonal antibody selected from the group consisting of J591, J533, E99, and J415 produced by hybridomas deposited under ATCC deposit accession numbers HB-12126, HB-12127, HB-12101, and HB-12109, respectively, an antigen-binding fragment thereof, a composition comprising said antibody or antigen-binding fragment, a kit for detecting prostate cancer comprising said antibody or antigen-binding fragment, and a hybridoma selected from the group consisting of the hybridomas deposited under ATCC deposit accession numbers HB-12126, HB-

12127, HB-12101, and HB-12109, and while being enabling for making and using an antibody or antigen binding fragment thereof described by the prior art, which is encompassed by the claims, a composition or kit comprising such an antibody or antigen binding fragment described by the prior art, as well as a hybridoma or other cell line producing such an antibody, does not reasonably provide enablement for making and/or using any antibody or antigen binding fragment that competes with a monoclonal antibody selected from the group consisting of E99, J415, J533 and J591 produced by hybridomas deposited under ATCC deposit accession numbers HB-12126, HB-12127, HB-12101, and HB-12109, respectively, for binding to PSMA, yet does not necessarily specifically bind to PSMA, an composition thereof, a kit for detecting any type of cancer comprising such an antibody or antigen-binding fragment thereof, or a cell that produces such an antibody. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The Office Action essentially reiterated the arguments presented under the Indefiniteness rejections regarding the determination of whether "the antibody 'competes' for binding to PSMA with any one of the recited monoclonal antibodies" and concludes that the specification "would not permit the skilled artisan to immediately identify antibodies that are suitable, and would not therefore reasonably enable the practice of the claimed invention without undue and/or unreasonable experimentation" (at page 27). The Office again cites George for its arguments (at pages 28-29).

As discussed supra, in the "Indefiniteness" section, Applicants submit that a determination of whether or not an antibody competes for binding with another antibody was a well-established procedure at the time of filing. In addition, interpretation of such assays to determine whether antibody competes or does not compete for binding was a well-established practice. George exemplifies this by making an affirmative decision that an antibody does or does not compete based upon that fact that a first antibody did not interfere within a reasonable margin of error for the binding of a second antibody to its antigen. A skilled artisan could easily make such a determination without undue experimentation.

For at least these reasons, Applicant requests that the rejection be withdrawn.

Rejections under 35 U.S.C. § 102

Claims 144, 156-161, 164, 171-173, and 178-210 are rejected at page 28 of the Office Action as being anticipated by U.S. Patent No. 6,962,981 as evidenced by Liu et al. (Cancer Res. 1998 Sep 15; 58:4055-4060) and George et al. (Circulation. 1998; 97:900-906).

The Applicant respectfully traverses this rejection. As discussed below, Murphy et al. is removed as prior art in light of the Declaration of Neil Bander, M.D. Under 37 CFR 1.131 (hereafter referred to as "the Bander declaration"), submitted herewith. This declaration was filed in U.S. Serial Number 09/357,704 to remove U.S. Patent Number 6,150,508 as a prior art reference. Since U.S. Patent No.: 6,962,981 is a continuation of U.S. Patent No.: 6,150,508, the Bander declaration should be sufficient with regards to U.S. Patent No.: 6,962,981 as well.

Murphy et al is not available as prior art against the present application because Applicant conceived the claimed invention prior to the priority date of the Murphy et al patent and diligently reduced it to practice. In particular, Murphy et al. has a priority date of March 25, 1996. As stated in the Bander declaration, Applicant conceived the claimed invention to practice prior to the priority date of the Murphy et al. patent and was diligent in reducing it to practice. Therefore, Murphy et al is not available as prior art against the present claims.

Claims 144, 156-158, 172, 173, 178, 180, 186, 187, 194, and 195 are rejected as being anticipated under 35 U.S.C. 102(b) by Liu et al. (Cancer Res. 1997 Sep 1; 57:3629-3634), as evidenced by Liu et al. (Cancer Res. 1998 Sep 15; 58:4055-4060) at page 31 of the Office Action. Applicants submit that none of these references precede the priority dates to which this application is entitled since the rejections under 112 are unfounded.

Claims 144, 156, 158, 172, 173, 180, 186, 187, 194, and 195 are rejected under 35 U.S.C. 102(b) as being anticipated by Israeli et al. (Cancer Res. 1994 Apr 1; 54(7):1807-1811) as evidenced by George et al. (Circulation. 1998; 97:900-906) at page 32 of the Office Action. The Office Action stated on page 33:

> Although Israeli et al. does not expressly teach the disclosed antibody "competes" for binding to PSMA with monoclonal antibodies J591, J415, J533, and/or E99, as

> evidenced by George et al. (cited supra), an antibody need not bind to the same epitope of an antigen as another antibody to measurably "compete" for binding to the antigen with the other antibody... Furthermore, although the specification teaches the antibody disclosed by Israeli et al. (monoclonal antibody 7E11) does not "compete" for binding to PSMA with any of monoclonal antibodies J591, J415, J533, and E99, neither the claims nor the disclosure delineate the conditions under which such a determination was made... [U]nder certain conditions, monoclonal antibody 7E11 is expected to "compete" to some measurable extent for binding to PSMA with monoclonal antibodies J591, J415, J533, and/or E99.

Applicants respectfully traverse this rejection. As discussed supra, in the "Indefiniteness" section, Applicants submit that a determination of whether or not an antibody competes for binding with another antibody was a well-established procedure at the time of filing. In addition, interpretation of such assays to determine whether antibody competes or does not compete for binding was a well-established practice.

Israeli et al. disclose a monoclonal antibody 7E11, which binds to the intracellular domain of PSMA. Within the art known meaning of "competes" for binding, monoclonal antibody 7E11 clearly does not compete for binding with the antibodies recited in the claims which bind the extracellular domain of PSMA. As such, Israeli et al. do not anticipate the claimed invention.

Claims 144, 156-161, 167, 170-173, 177, 178, 180, 184-203, 209, and 210 are rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,538,866 ("Israeli patent reference") as evidenced by George et al. (Circulation. 1998; 97:900-906) at page 33 of the Office Action. The Office Action at page 35 stated:

> [T]he disclosed antibodies bind the extracellular domain of PSMA, there is a reasonable presumption that the disclosed monoclonal antibodies also "compete" for binding to PSMA with one or more of the recited monoclonal antibodies...

First Applicants note that because the present application is entitled to its priority date, this is not a proper 102(b) rejection.

Further, it appears that the Examiner is making an inherency argument, pointing out that while Israeli does not teach all features of the present claim, it inherently anticipates them.

Applicants disagree. A reasonable presumption that Israeli's antibodies compete with the antibodies of the claimed methods is a mere possibility, not a necessary result. According to MPEP 2112. IV. and the Federal Circuit law, "[i]nherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient" (quoting *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999)). Further, "[i]n relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art" (MPEP 2112.IV, quoting *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990), emphasis in original). Israeli discloses ***hypothetical antibodies*** directed toward three, specific peptides (col. 6, lines 48-52), but does not teach or suggest that these antibodies compete for binding to PSMA with the antibodies of the claimed methods. Examiner's reasonable presumption that Israeli's hypothetical antibodies compete with the present antibodies does not prove that such competition necessarily flows from Israeli. Just because the hypothetical antibodies are directed against specific peptides of PSM antigen does not necessarily mean that they would compete with the present antibodies.

The peptides disclosed by Israeli are not capable of generating antibodies that bind PSMA; therefore, they cannot bind to PSMA and competes for binding to ~~prostate specific membrane antigen~~ ~~(~~PSMA~~)~~ with a monoclonal antibody as claimed. Applicants submit herewith as Exhibit B, Holmes (2001) *Exp. Opin. Invest. Drugs* 10(3): 511-519 ("Holmes"), which shows that the antibodies produced according to the techniques disclosed in Israeli do not bind to PSMA. Holmes teaches that rabbits were immunized with KLH-conjugates with aa63-68, aa132-137 or aa482-487 of PSMA. These correspond to SEQ ID 35, 36 and 37 as disclosed in Israeli. Holmes state that:

> No binding to full length PSMA could be demonstrated with these antisera under conditions that gave saturating peptide activity. Presumably, expression of these epitopes in the context of the protein was important and affected the antibody binding ability. This observation may be a property of the antibodies to these protein regions, or perhaps can be overcome by the use of slightly longer eight amino acids ..." (page 513, first column, lines 6-14).

From Holmes, it is clear that antibodies generated to the peptide disclosed in Israeli do not bind to PSMA, and thus would not compete for binding to PSMA with the antibodies recited in the claims.

Israeli also discusses polyclonal and monoclonal antibodies that generally bind to PSM antigen, without reciting any further characteristics of such antibodies (col. 6, lines 48-52). These antibodies are even further removed from the present antibodies. In fact, these Israeli's antibodies can be at best described as a genus of antibodies that bind to PSMA, and as such they do not anticipate the species of antibodies of the claimed methods. According to MPEP 2112.IV, "a prior art reference that discloses a genus still does not inherently disclose all species within that broad category" (quoting *Metabolite Labs v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1367 (Fed. Cir. 2004)). Thus, Israeli's monoclonal and polyclonal antibodies directed against PSM antigen are a broad genus that cannot anticipate the present antibodies produced by specific recited hybridomas.

The Office Action also stated at pages 34 and 35:

> as evidenced by George et al. (cited *supra*), an antibody need not bind to the same epitope of an antigen as another antibody to measurably "compete" for binding to the antigen with the other antibody. Thus, at a high enough concentration, or under certain conditions, *any* antibody, including an antibody that binds to a different epitope of an antigen than the epitope recognized by another antibody that binds the antigen is expected to "compete" for binding to the antigen with the other antibody . . . [T]he antibodies disclosed by the prior art are polyclonal; polyclonal antibodies raised against PSMA bind a plurality of epitopes of PSMA, and are reasonably expected to comprise one or more species of antibody that bind to the same epitopes as monoclonal antibodies J591, J415, J533, and/or E99 and thereby "compete" for binding to PSMA with one or more of the monoclonal antibodies (emphasis added).

Applicants disagree. First, as discussed in depth above, competition assays were well-known in the art at the time of filing the application. Skilled practitioners, such as George, knew how to carry out controlled experiments to avoid false positives and determine which results constitute competition at the time of filing the present application.

Second, as discussed above, polyclonal antibodies taught by Israeli are a broad genus that does not anticipate the specific antibodies of the claimed methods. The Office seems to acknowledge that Israeli's polyclonal antibodies are a genus, when it states that they "are reasonably expected to comprise one or more species of antibody that bind to the same epitopes" as the instant antibodies (see quote above). A reasonable expectation is a mere possibility (not a necessary characteristic) that the broadly described polyclonal antibodies would compete for binding with the antibodies of the claimed methods. Thus, Israeli's polyclonal antibodies do not anticipate the present antibodies.

At least for the reasons presented above, Applicants respectfully request that all anticipation rejections be withdrawn.

Claims 144, 156-168, and 170-210 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent Application Publication No. 2004/0213791 or U.S. Patent Application Publication No. 2004/0120958. The Office Action stated at page 37 that

> U.S. Patent Application Publication No. 2004/0120958 A1 is a continuation-in-part of the earlier filed application, namely copending Application No. 10/379,838, which is a continuation-in-part of another earlier filed application, which was published as the above cited U.S. Patent Application Publication No. 2004/0213791 A1. Accordingly, absent a showing otherwise, it is submitted that U.S. Patent Application Publication No. 2004/0120958 A1 teaches the subject matter taught by U.S. Patent Application Publication No. 2004/0213791 A, which has been incorporated in its entirety by reference therein, and therefore provides a disclosure that anticipates the inventions of claims 144, 156-168, and 170-210.

Applicant submits that the claims are entitled to the earliest priority date available for this application. The earliest priority dates on both of these patent applications is June 1, 2001 (for 2004/0213791 A1). The earliest priority dates of the present application are before this date. Applicant respectfully requests that this rejection be withdrawn in view of arguments made in rebuttal of rejections made under 35 U.S.C. § 112.

Claims 144, 156-168, and 170-210 are provisionally rejected under 35 U.S.C. 102(e) as being anticipated by copending Application No. 10/379,838 which has a common inventor with the instant application. The Office Action stated at page 37 that

> based upon the earlier effective U.S. filing date of the copending application, it would constitute prior art under 35 U.S.C. 102(e), if published under 35 U.S.C. 122(b) or patented. This provisional rejection under 35 U.S.C. 102(e) is based upon a presumption of future publication or patenting of the copending application.

Applicant submits that the claims are entitled to the earliest priority date available for this application. The earliest priority date on this patent application is June 1, 2001. The earliest priority dates of the present application are before this date. Applicant respectfully requests that this rejection be withdrawn in view of arguments made in rebuttal of rejections made under 35 U.S.C. § 112.

Conclusion

Applicant respectfully submits that all claims are in condition for allowance, which action is expeditiously requested. Applicant does not concede any positions of the Examiner that are not expressly addressed above, nor does Applicant concede that there are not other good reasons for patentability of the presented claims or other claims.

Enclosed is a Petition for a Three-Month Extension of Time. The required fee is being paid concurrently herewith on the Electronic Filing System (EFS) by way of Deposit Account authorization. Please apply any other charges or credits to Deposit Account No. 06-1050, referencing attorney docket no. 21052-003009.

Respectfully submitted,

Date: 10/11/07

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